REMARKS

Reconsideration of the application is respectfully requested for the following reasons:

1.   Rejection Under 35 USC §112, 2nd Paragraph

   A.   Appearance Frequency Information

The objection to "appearance frequency information" has been addressed by specifying that the appearance frequency is simply the frequency at which the designated domain combination appears. Appearance frequency *information* is information (or data) concerning the "frequency of appearance."

Those skilled in the art will understand that frequency of appearance refers to how often (*i.e.*, how "frequent") the domain combination appears during a given interval. It might appear ten times per interval, or twenty times. The number of times an event occurs is commonly known as the "frequency," although the term "probability" could also be used. It is respectfully submitted that this is not an ambiguous concept, and that the phrases *"information concerning frequency of appearance"* and *"appearance frequency information,"* can be easily understood by those skilled in the art.

As to application to interacting and non-interacting pairs, it is respectfully submitted that the designated domain combinations are selected from *both* interacting and non-interacting protein pairs, as explained for example in lines 21-23 on page 8 of the original specification, and that the frequency information concerns designated domain combinations that contain both interacting and non-interacting sets of protein pairs (the global set within which interaction probability is predicted). There is no conflict between the initial gathering of information concerning the frequency at which designated domain combinations appear and the subsequent determination of an interaction probability value. To the contrary, when the process is started, one does not even know the interaction probability value and therefore must start with both interacting and non-interacting pairs.

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Accordingly, it is respectfully submitted that the frequency of appearance of "appearance frequency" is unambiguous and proper under 35 USC §112, 2nd Paragraph.

B.   Interaction

The objection to the word "interaction" is respectfully traversed on the grounds that the invention applies to *any* protein-protein interaction, and that it is not reasonable to require the invention to be limited to a particular type of interaction. The invention logically can be applied to "chemical" interactions, enzymatic interactions (which are also "chemical" interactions), hydrogen bonds (which is a type of "chemical" interaction), and so forth. Those skilled in the art will understand that an interaction occurs when one protein affects another protein, *i.e.*, when there is "*mutual or reciprocal action or influence*" as defined in Webster's Ninth New Collegiate Dictionary, and that there are a finite number of such interactions depending on the types of protein involved, and that the frequency of interactions, *i.e.*, the number of interactions that occur in a given interval, can be determined for any of the interactions.

The fact that proteins can interact in different ways (although fundamentally, the interactions actually come down to a few fundamental forces) does not render ambiguous the concept of counting the number of "interactions" in a given interval (frequency or probability of appearance) using the steps specifically set forth in the claim. It is a fundamental principle of patent practice that claims are not required to be limited to particular examples, but rather may cover multiple embodiments or possibilities. A claim that recites a fastener as part of a combination is not indefinite just because there are numerous different fasteners (some of which might not even be useful in the claimed combination). Similarly, recitation of protein interactions does not render indefinite the recitation of interacting and non-interacting protein pairs.

As to the alleged conflict between recitation of interacting and non-interacting protein pairs, it is respectfully submitted that it is not at all unclear how one can take into account non-

interacting pairs in determining the frequency of interaction. The number of pairs that do not interact is just as relevant to the interaction probability as the number of pair that do interact. According to the Examiner's "logic," it does not make sense to count the number of "tails" when flipping a coin in order to determine the probability that "heads" will appear. In reply, the Applicant respectfully submits that one can obtain the probability that heads will appear by counting both heads and tails, and that the interaction probability for protein pairs can be determined by taking into account both the pairs that interact and the pairs that do not interact. In fact, if one only takes into account pairs that interact and ignores other pairs, the interaction probability will be "1," which makes no sense.

Finally, it is respectfully noted that the Examiner apparently has no trouble understanding the term "interaction" (or frequency) as used in the Gomez article applied in the Official Action under 35 USC §102, even though the method of Gomez, like that of the claimed invention, clearly can be applied to protein - protein interactions other than the specific example given in part 3. If the description in the Gomez article is inadequate, then it cannot anticipate the claimed invention. If it is adequate, then so is the description of the presently claimed invention.

C.   Designated

Although the word "designated" is not ambiguous, but to the contrary is easily understood by those skilled in the art as well as in ordinary speech (it means "*to indicate and set apart for a specific purpose*"), claim 1 has been amended to delete the word "designated." As will "interaction," it does not matter how a domain combination is designated, and the requirements of 35 USC §112 are easily satisfied by the examples given in the specification. There is absolutely no logical reason why the invention should be arbitrarily limited to particular ways of designating domain combinations.

D.   Each

This grounds for rejection has been addressed by deleting the word "each" and instead spelling out that the domain combination pair is selected from an interacting set and a non-interacting set.

F.   Interaction Between Two Proteins

This grounds for rejection has been addressed by clarifying that the two proteins are proteins of the selected domain combination pair.

G.   Determining

This grounds for rejection has been addressed by changing "determining" to "defining."

H.   Equation Applied to Predict

This grounds for rejection has been addressed by deleting the word "applying."

I.   Equations

The equation in claim 3 has been clarified by defining WF, dc(p), and dc(q) according to the definitions respectively given in lines 13-23 on page 7 and lines 14-19 on page 5 of the original specification.

2.   Rejection of Claims 1-4 Under 35 USC §101 (item 4 on page 5 of Official Action)

This rejection is respectfully traversed on the grounds that prediction of interaction probability does not require identification of which interaction is being addressed. To the contrary, the invention is a statistical analysis that distinguishes between interacting and non-interacting pairs, but does not seek to identify particular interactions. In fact, it is not clear that an analysis that takes into account certain interactions and not others would even be practical using the claimed method.

In part B of item 3 on page 3 of the Official Action, the Examiner identifies four types of protein interactions. There is no logical reason why the invention should be arbitrarily limited to just one of those four types of interactions. Proteins can only interact in a finite number of ways, and the Applicant intends to cover any such interactions, depending only on the types of proteins being analyzed. While the specification describes yeast proteins as an example, the method is clearly applicable to other types of proteins.

Not only does it not make sense to limit the invention, which does not depend on the nature of the interactions, to a particular type of interaction, but the Official Action itself points out that a method that requires information about function interaction between known domains is "severely limited" (see the first complete sentence on page 6 of the Official Action). The invention avoids the problems noted by the Examiner in connection with the Gomez article by taking a different approach that does not seek to combine frequency information with information about functional interaction. This is not a case of an unidentified variable, but rather involves a variable (probability of interactions) that may have multiple possibilities or embodiments.

In view of the above, withdrawal of the first rejection under 35 USC §101 set forth on page 5-6 of the Official Action is respectfully requested.

3.   Rejection of Claims 1-4 Under 35 USC §112, 1st Paragraph and Under 35 USC §101, as set forth on pages 7-10 of the Official Action

These rejections are apparently on the basis that prediction of the interaction between proteins is not a useful, tangible, and concrete result.

In reply, the Applicant respectfully points out, as explained in the introductory portion of the present application, that almost all reactions, such as signal transduction, cell life cycle, differentiation, DNA replication, transcription and translation, metabolism, and so forth that occur in cells depend on the interactions of proteins, and that a great deal of research into

biochemical development and mechanisms in cells is based on analyzing and especially predicting the interactions between proteins. As a result, numerous articles have been published concerning methods of predicting the interactions, usually by analyzing the physiochemical properties or tertiary structures of the proteins, but also by domain based protein-protein interactions prediction. **Given all of the research into protein interaction prediction, and the numerous publications describing methods of prediction, it is not understood how the Examiner can characterize such "prediction" as not useful, tangible, or concrete.** This characterization makes no sense. Are all of the researchers and authors devoted to prediction of protein interactions wasting their time?

Paradoxically, the Examiner not only indicates that the invention lacks utility, but also alleges that it is anticipated by the Gomez article. While the Gomez article in fact does not anticipate the claimed invention, as explained below, it does show the utility of the invention, both because of its explanation of the usefulness of prediction to the biology community (see pages 413 and 414), and also because the method of Gomez is not dependent on a particular interaction but rather applies to any protein - protein interaction.

All of the claims of the present application specifically recite prediction of protein interactions. Proteins are tangible substances, and interactions are tangible events. Prediction of such events is useful for numerous purposes. How, then, can such prediction be said to lack utility? The claimed invention involves some mathematical steps, but they are applied to **tangible elements** (protein pairs) to obtain a **useful and tangible result** (interaction probability prediction). Therefore, it is respectfully submitted that the invention as claimed has utility, and withdrawal of the rejections of claims 1-4 under 35 USC §§101 and 112, 1st Paragraph are improper and should be withdrawn.

4..   <u>Rejection of Claims 1, 2, and 4 Under 35 USC §102(b) in view of *"Towards The Prediction Of Complete Protein - Protein Interaction Networks,"* Pacific Symposium on Biocomputing 2002 (Gomez)</u>

This rejection is respectfully traversed on the grounds that the prediction method of Gomez, while domain based, fails to disclose or suggest the following:

- selecting a domain *combination* pair from an interacting set and a non-interacting set of protein pairs, as recited in original and amended claim 1 (Gomez only considers the interactions of single domain pairs);

- performing the frequency information storing and probability equation defining steps on the domain *combination* pair rather than single domain pairs, as recited in original and amended claim 1 (Gomez performs corresponding steps on single domain pairs); and

- defining the probability equation by determining a function which maps the selected domain combination pair to a real number; and generating and storing a prediction distribution having values obtained by applying the determined function to a protein pair which configures the interacting and non-interacting sets of protein pairs, as recited in amended claim 1 (Gomez does not disclose either of these sub-steps for defining the probability equation, but rather seeks to take into account functional interaction between known domains, as pointed out in the paragraph bridging pages 5 and 6 of the Official Action).

By selecting domain combination pairs in the manner claimed, defining the probability equation with respect to the pairs, based on a prediction distribution having values obtained by applying a mapping function to a protein pair which configures interacting and non-interacting sets of protein pairs, as is now claimed, the invention overcomes the limitation of Gomez' method that is caused by information about functional interaction between the known domains. Accordingly, while the Gomez article supports the utility of the present invention, it does not anticipate it, and withdrawal of the rejection of claims 1, 2, and 4 under 35 USC §102(b) is respectfully requested.

It is noted that claim 3 has not been rejected on prior art, and therefore an explicit indication of allowability over the prior art would be appreciated.

Having thus overcome each of the rejections made in the Official Action, withdrawal of the rejections and expedited passage of the application to issue is requested.

Respectfully submitted,

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